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(54) Title: VITAMIN B6 RELATED COMPOUNDS AND METHODS FOR RECOVERY FROM TRAUMA

(57) Abstract: The present invention provides a method of promoting recovery from trauma in a patient in need thereof comprising the administration of a therapeutically effective amount of a vitamin B6 related compound (excluding vitamin B6), preferable compounds include pyridoxal-5-phosphate, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxy-4,5-animal and pyridoxine phosphate analogues.



**WO 2006/026868 A1**

**TITLE:** Compounds and Methods for Recovering from Trauma

**FIELD OF INVENTION**

**[0001]** The present invention relates to compositions useful for the treatment of a traumatic injury, and in particular surgical traumatic injury.

**BACKGROUND**

**[0002]** Patients who suffer from an adverse physiological event such as stroke or myocardial infarction suffer traumatic injury resulting from damage to the vasculature. In such cases, the patient generally undergoes a surgical procedure to treat the damage resulting from the adverse event or to prevent further occurrences of the adverse event. Surgical intervention in and of itself is a form of further traumatic injury. It is desirable to improve functional recovery from such traumatic injury by either increasing the rate of recovery or by increasing the extent of recovery such that the functionality of the tissue and/or organ damaged as a result of the traumatic injury is close to or equal to its functionality prior to the traumatic injury. By improving tissue or organ function following a traumatic injury, or by increasing the rate of such recovery, or both, the affected patient's quality of life is greatly improved by reducing discomfort associated with repair of the damaged tissue and/or organ, reducing the number of days spent in hospital and reducing the associated stress of undergoing treatment.

**[0003]** Currently, there is no safe and cost-effective pharmaceutical treatment, which reliably improves the prognosis of an individual who has suffered from a traumatic injury resulting from damage to the vasculature, and in particular a traumatic injury resulting from surgical intervention.

**SUMMARY OF INVENTION**

**[0004]** The present invention provides a method of promoting patient recovery from trauma comprising administering a therapeutically effective amount of a vitamin B6 related compound.

**[0005]** In an embodiment of the invention, the vitamin B6 related compound is pyridoxal-5'-phosphate.

**[0006]** In a further embodiment of the invention, the vitamin B6 related compound is selected from a group comprising: pyridoxine, pyridoxal, pyridoxal-5'-phosphate, pyridoxamine, a 3-acylated analogue of pyridoxal, a 3-acylated analogue of pyridoxal-4,5-aminal, a pyridoxine phosphate analogue, and a mixture thereof.

**[0007]** In yet another embodiment of the invention, the trauma is caused by an adverse physiological event selected from a group consisting of: myocardial infarction, myocardial ischemia, ischemic stroke, hemorrhagic stroke, major cardiac trauma, hypertension, arteriosclerosis, aneurysm, and congestive heart failure.

**[0008]** In a still further embodiment of the invention, the trauma is the result of a traumatic contact suffered by the patient, the traumatic contact selected from a group consisting of: abrasion, incision, contusion, puncture, and compression.

**[0009]** In another embodiment of the invention, the trauma is a surgical trauma. The surgical trauma may be the result of a surgical procedure selected from a group consisting of: coronary bypass surgery, biopsy, heart valve replacement, atheroectomy, thrombectomy, transcatheter vascular therapy, angioplasty, vascular grafting, placement of a mechanical shunt, placement of an intravascular stent, and organ transplantation.

**[00010]** In a further embodiment of the invention, the vitamin B6 related compound is administered prior to, during, and/or following the surgical procedure.

#### **BRIEF DESCRIPTION OF THE FIGURES**

**[00011]** Table 1 summarizes the baseline characteristics, length of hospitalization, and time to discharge from initiation of percutaneous coronary

intervention (PCI) in patients treated with pyridoxal-5'-phosphate (P5P) and with placebo.

### **DETAILED DESCRIPTION**

**[00012]** The present invention is based upon the surprising discovery that functional recovery following a traumatic injury is significantly enhanced by the administration of pyridoxal-5'-phosphate, a vitamin B6 related compound.

**[00013]** The invention provides methods of treating a traumatic injury. In one aspect, the present invention provides a method of promoting recovery from trauma in a patient in need thereof, comprising administering a therapeutically effective amount of pyridoxal-5'-phosphate (P5P) or another vitamin B6 related compound.

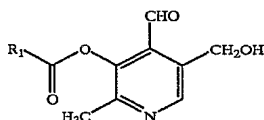
**[00014]** As used herein, the term "promoting recovery" refers to the promotion of a clinically significant improvement to the physiological damage resulting from the traumatic injury.

**[00015]** While the exact mechanism for the trauma recovery promoting effects of vitamin B6 related compound is not known, the present inventors have found that administration of vitamin B6 related compounds increases the rate of recovery from trauma. Without being limited to one particular theory, the beneficial effects of vitamin B6 related compounds may be due in part to the compounds' abilities to promote tissue regeneration at the site of damage. The present inventors have previously shown the effectiveness of vitamin B6 related compounds for the treatment of various cardiovascular diseases (see for example US Patent No. 6,417,204 and 6,677,356). However, a surprising finding is that vitamin B6 related compounds are not only able to treat the adverse event caused by such diseases, they are also able to reduce or treat trauma.

**[00016]** As used herein, the term "vitamin B6 related compound" means any vitamin B6 related precursor, metabolite, derivative or analogue but excludes vitamin

B6 (pyridoxine). In a preferred embodiment, the vitamin B6 related compound used to practice the invention is pyridoxal-5'-phosphate (P5P). Other vitamin B6 related compounds which can also be used to practice the invention, include the 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4, 5-aminal, and pyridoxine phosphonate analogues described in US Patent No, 6,585,414 and US Patent Application No. 20030114424.

**[00017]** The 3-acylated analogues of pyridoxal include:



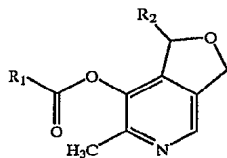
wherein,

R<sub>1</sub> is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxycarbonyl, or

R<sub>1</sub> is dialkylcarbamoxyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxycarbonyl; dialkylcarbamoxyloxy; or

R<sub>1</sub> is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy.

**[00018]** The 3-acylated analogues of pyridoxal-4,5-aminal include:



wherein,

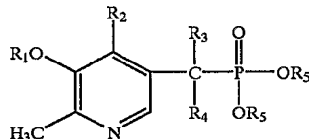
R<sub>1</sub> is alkyl, alkenyl, in which alkyl can be interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxy carbonyl, or

R<sub>1</sub> is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxy carbonyl; dialkylcarbamoyloxy; or

R<sub>1</sub> is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

R<sub>2</sub> is a secondary amino group.

**[00019]** The pyridoxine phosphate analogues include:



(a)

wherein,

R<sub>1</sub> is hydrogen or alkyl;

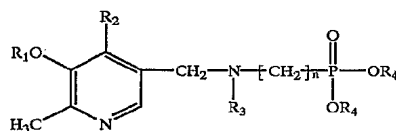
R<sub>2</sub> is -CHO-, -CH<sub>2</sub>OH, -CH<sub>3</sub>, -CO<sub>2</sub>R<sub>6</sub> in which R<sub>6</sub> is hydrogen, alkyl, aryl; or

R<sub>2</sub> is -CH<sub>2</sub>-O alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of R<sub>1</sub>;

R<sub>3</sub> is hydrogen and R<sub>4</sub> is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino, or arylamino; or

R<sub>3</sub> and R<sub>4</sub> are halo; and

R<sub>5</sub> is hydrogen, alkyl, aryl, aralkyl, or -CO<sub>2</sub>R<sub>7</sub> in which R<sub>7</sub> is hydrogen, alkyl, aryl, or aralkyl;



(b)

wherein,

R<sub>1</sub> is hydrogen or alkyl;

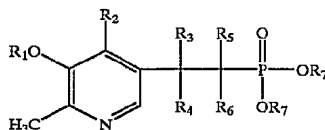
R<sub>2</sub> is -CHO, -CH<sub>2</sub>OH, -CH<sub>3</sub>, -CO<sub>2</sub>R<sub>5</sub> in which R<sub>5</sub> is hydrogen, alkyl, aryl; or

R<sub>2</sub> is -CH<sub>2</sub>-O alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of R<sub>1</sub>;

R<sub>3</sub> is hydrogen, alkyl, aryl, aralkyl,

R<sub>4</sub> is hydrogen, alkyl, aryl, aralkyl, or -CO<sub>2</sub>R<sub>6</sub> in which R<sub>6</sub> is hydrogen, alkyl, aryl or aralkyl;

n is 1 to 6; and



(c)

wherein,

R<sub>1</sub> is hydrogen or alkyl;

R<sub>2</sub> is -CHO-, CH<sub>2</sub>OH-, -CH<sub>3</sub>, -CO<sub>2</sub>R<sub>8</sub> in which R<sub>8</sub> is hydrogen, alkyl, aryl; or

R<sub>2</sub> is -CH<sub>2</sub>-O alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R<sub>1</sub>;

R<sub>3</sub> is hydrogen and R<sub>4</sub> is hydroxy, halo, alkoxy, or alkanoyloxy; or

R<sub>3</sub> and R<sub>4</sub> can be taken together to form =O;

R<sub>5</sub> and R<sub>6</sub> are hydrogen; or

R<sub>5</sub> and R<sub>6</sub> are halo;

R<sub>7</sub> is hydrogen, alkyl, aryl, aralkyl, or -CO<sub>2</sub>R<sub>8</sub> in which R<sub>8</sub> is hydrogen, alkyl, aryl, or aralkyl.

**[00020]** Some of the compounds described herein contain one or more asymmetric centres and this may give rise to enantiomers, diastereomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (R)- or (S)-. The present invention is meant to include all such possible diastereomers and enantiomers as well as their racemic and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centres of geometric symmetry, and unless specified otherwise, it is intended that the compounds include both E and A geometric isomers. Likewise all tautomeric forms are intended to be included.

**[00021]** The invention is expected to be useful for treating a variety of traumatic injuries. The "traumatic injury" or "trauma" may be the result of tissue damage



caused by an abrasion, incision, contusion, puncture, compression, etc. arising from traumatic contact with a foreign object such as during an accident or during a surgical procedure such as coronary bypass surgery, biopsy, heart valve replacement, atheroectomy, thrombectomy, transcatheter vascular therapy, angioplasty, vascular grafting, placement of a mechanical shunt, placement of an intravascular stent, or an organ transplantaton. The "traumatic injury" or trauma may be the result of tissue damage caused by burns including chemical and radiation burns. The "traumatic injury" or "trauma" may be the result of tissue damage caused by an adverse physiological event such as myocardial infarction, myocardial ischemia, ischemic stroke, hemmorhagic stroke, major cardiac trauma, hypertension, arteriosclerosis, aneurysm, or congestive heart failure.

**[00022]** In practice, a patient suffering a traumatic injury is administered a therapeutically effective amount of vitamin B6 related compound shortly after the occurrence of the injury or the appearance of symptoms suggestive of a traumatic injury. In the case of "planned" traumatic injury, such as a scheduled surgical procedure, the patient may, in addition or in alternative, be administered a therapeutically effective amount of vitamin B6 related compound shortly before, or during, the planned trauma. The terms "effective amount" or a "therapeutically effective amount" of a compound refers to a nontoxic but sufficient amount of the compound to provide the desired effect. In the present invention, the "effective amount" of the vitamin B6 related compound is the amount that is effective to promote recovery from the traumatic injury. The amount that is effective will vary from subject to subject, and will depend on a number of factors which will be apparent to those skilled in the art and in light of the disclosure herein. In particular, these factors include: the identity of the compounds to be administered, the formulation, the route of administration employed, the patient's gender, age, and weight and the severity of the condition being treated and the presence of concurrent illness. Thus, it is not always possible to specify an exact "effective amount". However, an appropriate effective amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation. Methods for

determining dosage and toxicity are well known in the art with studies generally beginning in animals and then in humans.

**[00023]** Where the vitamin B6 related compound employed is P5P, the typical therapeutic is between 1 to 1000 mg per kg patient per day. The preferred route of administration of the vitamin B6 related compound will depend on the particular traumatic injury to be treated and may include: oral administration, rectal administration, parental injection, and intravenous injection. It may be desirable to administer the vitamin B6 related compound with an appropriate pharmaceutically acceptable diluent or carrier known in the art.

**[00024]** In a preferred embodiment, the invention provides a method of promoting recovery from a surgical trauma in patient in need thereof, comprising the administration of a vitamin B6 related compound, and more preferably P5P. In a further preferred embodiment, the invention provides a method of promoting recovery from a surgical trauma resulting from surgical intervention to the cerebrovascular or cardiovascular system. The surgical trauma may include vascular trauma to the macrovasculature, microvasculature and/or the heart muscle.

**[00025]** Examples of surgical vascular traumas include, but are not limited to: (1) vascular surgery, such as coronary bypass surgery, biopsy, heart valve replacement, atheroectomy, thrombectomy, and the like; (2) transcatheter vascular therapies (TVT) including angioplasty, e.g., laser angioplasty and PTCA procedures employing balloon catheters, and indwelling catheters; (3) vascular grafting using natural or synthetic materials, such as in saphenous vein coronary bypass grafts, dacron and venous grafts used for peripheral arterial reconstruction, etc.; (4) placement of a mechanical shunt, such as a PIFE hemodialysis shunt used for arteriovenous communications; (5) placement of an intravascular stent, which may be metallic, plastic or a biodegradable polymer; and (6) organ transplantation, such as heart, kidney, liver and the like. Since the success of the post-operative recovery from surgical interventions such as the ones described herein is often a measure of

the success of the surgery itself, treatment with B6 related compounds can improve the overall outcomes of such surgical procedures.

**[00026]** Individuals which maybe treated using the invention include those individuals about to undergo, undergoing or having undergone surgery. Administration of the vitamin B6 related compound may be initiated several days to weeks, prior to scheduled surgery and may be continued to and through the surgical procedure. Administration may also continue for several days to weeks or months post-surgery. For unscheduled surgery, the treatment may commence as soon as feasible prior to and throughout the surgical procedure.

**[00027]** In one embodiment, where the individual to be treated is undergoing vascular surgery, it is preferable to administer between 10 mg/kg patient weight and 30 mg/kg patient weight of P5P prior to the surgery. In a further preferred embodiment, the individual undergoing vascular surgery is administered 10 mg/kg of P5P orally at least 4 hours prior to the surgery and 10 mg/kg patient weight of P5P daily for at least 14 days following the surgery.

**[00028]** It may be desirable in certain circumstances to administer the vitamin B6 related compound in combination a cardioprotective agent following vascular surgery. Examples of cardioprotective agents which may be administered with the vitamin B6 related compound in order to promote trauma recovery include platelet aggregation inhibitor such as: thromboxane A<sub>2</sub> inhibitors (e.g. acetylsalicylic acid (ASA)), glycoprotein IIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban, lamifiban, xemilofiban, orbofiban, sibrafiban, fradafiban, roxifiban, lotrafiban), adenosine phosphate inhibitors (e.g. clopidogrel, dipyridamole, sulfinpyrazone), fibrinogen-platelet binding inhibitors (ticlopidine), or a platelet c-AMP phosphodiesterase inhibitor, such as dipyridamole or cilostazol, or pentoxifylline (trental).

**[00029]** The vitamin B6 related compounds and the platelet aggregation inhibitors can be administered concurrently or successively following surgery.

Therapeutically effective dosages for the platelet inhibitors discussed above are well known in the art. It may also be possible to slightly decrease the therapeutically effective dosage of platelet inhibitor (thus reducing the side effects of such treatment) as a result of the combination therapy with vitamin B6 related compound, due to the improved trauma recovery or speed of recovery that is a result of the vitamin B6 related compound treatment.

**[00030]** Although the invention has been described with reference to illustrative embodiments, it is to be understood that the invention is not limited to these precise embodiments, and that various changes and modifications may be effected therein by one skilled in the art. All such changes and modifications are intended to be encompassed in the appended claims.

**[00031]      Example One - P5P Promotes Rapid Recovery Following PCI**

**[00032]**      Selection of Study Population - The patients selected for this trial were patients scheduled for elective percutaneous coronary intervention (PCI) with high-risk features for periprocedural myocardial infarction, and who satisfied specific inclusion criteria as described in the next section. Patients to be included in this study were of either sex, > 18 years of age and admitted to hospital for elective, single-vessel, non-urgent PCI. Patients must have presented with at least one of the following high-risk clinical criteria:

- ACS with last chest pain episode (or ischemic equivalent) within 48 hours,
- recent myocardial infarction ( $\leq 7$  days) with return of cardiac markers, (CK, CK-MB, and troponin) to below upper normal limits,
- angiographic evidence of reduced epicardial flow (TIMI < 3),
- angiographic evidence of thrombus,

- left ventricular ejection fraction  $\leq$  30%, or
- saphenous vein graft lesion.

**[00033]** The following patients were not eligible for inclusion into the study:

- Those having suffered a recent myocardial infarction with elevated cardiac markers (CK-MB, troponin T), that have not returned to below upper limits or normal;
- Those with electrocardiographic evidence of left bundle branch block (LBBB), ventricular paced rhythm, or atrial fibrillation;
- Those with a planned multivessel PCI or PCI of known total occlusion (TIMI grade 0);
- Those with evidence of ongoing or active clinical instability including; sustained systolic blood pressure < 90 mmHg, cardiogenic shock, acute pulmonary edema or severe congestive heart failure, suspected acute myocarditis, pericarditis, endocarditis, cardiac tamponade, suspected dissecting aortic aneurysm, hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease;
- Any contraindication to the PCI procedure or any of the standard concomitant therapies used during routine PCI (e.g. aspirin, clopidogrel, heparin, low molecular weight heparin, direct antithrombin inhibitors, platelet glycoprotein IIb/IIIa antagonists);
- Patients who were currently enrolled in a clinical trial of an investigational drug or who have participated in a clinical trial for an investigational drug (a new

chemical entity not registered for clinical use) within 30 days preceding entry into the study or who are due to enter such a trial during the study period;

- Patients with clinically significant abnormal laboratory findings (within 2 weeks prior to PCI) including: ALT, AST, bilirubin, or Alk Phos > 1.5x ULN, Serum creatinine > 1.8 mg/dL or 159 µmol/L;
- Patients with any other pathology such as cancer, mental illness etc., which in the opinion of the investigator, might put the patient at risk or confound the results of the trial;
- Female patients who are pregnant, breast feeding or planning a pregnancy during the course of the study; and
- Patients who are unable or unwilling to comply with the protocol or who are not expected to complete the study period.

**[00034] Treatments Administered** - Following baseline laboratory assessments, patients were randomized to placebo or P5P (a vitamin B6 related compound), administered as a 10 mg/kg oral dose, at least (4) hours prior to PCI, followed by 10 mg/kg orally divided in two daily doses for fourteen (14) days. If PCI was delayed for more than 12 hours after initial dosing, they continued with scheduled BID dosing. If the initial loading dose was administered prior to or at 12:00 PM on day 1 of randomization, then the patient received a second evening dose. If the initial loading dose was administered following 12:00 PM, then no further dosing was administered on day 1, and the patient was to begin the next dose in the morning of day 2. If a dose was missed for more than 24 hours, patients were to continue to take the study drug as scheduled without taking supplemental doses. The date, time and dosing of the first and last study drug dosing was recorded in the CRF. Doses missed within a 24-hour period were to be amended by taking the scheduled

dose for that day. Compliance was recorded as the number of tablets dispensed to the patient and returned to the site at the end of the study.

**[00035] Selection and Timing of Dose for Each Patient** - Following baseline laboratory assessments, patients were to be randomized to placebo or P5P administered as a 10 mg/kg oral dose given, at least (4) hours prior to PCI. This was followed by 10 mg/kg orally divided in two daily doses for fourteen (14) days. If the PCI was delayed for more than 12 hours after the initial dose, the patient continued with scheduled BID dosing. Also, if the initial loading dose was administered prior to or at 12:00 PM on day 1 of randomization, then the patient was to receive a second evening dose. If the initial loading dose was administered following 12:00 PM, then no further dosing was to be administered on day 1, and the patient should begin the next dose in the morning of day 2. If a dose was missed for more than 24 hours, patients continued to take the study drug as scheduled without taking supplemental doses. The date, time and dosing of the first and last study drug dosing was recorded in the CRF. Doses missed during a 24-hour period were amended, by taking the scheduled dose for that day. Compliance was recorded as the number of tablets dispensed to the patient and returned to the site at the end of the study.

**[00036] Prior and Concomitant Therapy** - At the time of PCI, all patients received 325 mg of aspirin and 300 mg of clopidogrel. Heparin was also administered in accordance with local standard of care. Thereafter, and for the next 30 days patients received 325 mg aspirin and 75 mg of clopidogrel daily. The choice of GP IIb/IIIa inhibition and additional medications was left to the discretion of the physician.

**[00037] Results** - Table 1 shows the baseline characteristics of patients participating in the study by treatment group. Patients randomized to P5P were treated 3 times more quickly (9.4 hours versus 31 hours), and were in hospital only half as long (3.3 days versus 7.0 days) as those given placebo. The number of days from initiation of the PCI procedure to discharge from the hospital was 74% shorter in patients treated with P5P versus those treated with placebo.

Table 1 – Comparison of baseline characteristics, length of hospitalization and time to discharge from initiation of PCI in patients treated with P5P and placebo

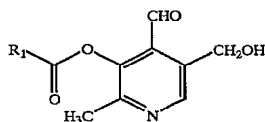
	P5P (N = 40)	Placebo (N=20)	All Patients (N = 60)
Number of Diseased Vessels			
0	1/40 (2.5%)	0/20	1/60 (1.7%)
1	19/40 (47.5%)	14/20 (70.0%)	33/60 (55.0%)
2	13/40 (32.5%)	2/20 (10.0%)	15/60 (25.0%)
3	5/40 (12.5%)	3/20 (15.0%)	8/60 (13.3%)
Left Main	2/40 (5.0%)	1/20 (5.0%)	3/60 (5.0%)
Primary reason for PCI			
ACS	9/38 (23.7%)	5/20 (25.0%)	14/58 (24.1%)
Recent MI	16/38 (42.1%)	3/20 (15.0%)	19/58 (32.8%)
Reduced epicardial flow	6/38 (15.8%)	8/20 (40.0%)	14/58 (24.1%)
Thrombus	1/38 (2.6%)	1/20 (5.0%)	2/58 (3.5%)
LVEF <= 30 percent	2/38 (5.3%)	1/20 (5.0%)	3/58 (5.2%)
Saphenous vein graft lesion	4/38 (10.5%)	2/20 (10.0%)	6/58 (10.3%)
Length of hospitalization (days)			
N (Missing)	40(0)	20(0)	60(0)
Mean (S.D.)	3.3(5.5)	7.0(9.9)	4.5(7.4)
Median (25 <sup>th</sup> , 75 <sup>th</sup> )	1.0(1.0, 3.0)	3.0(1.0, 8.5)	1.5(1.0, 5.0)
Minimum, Maximum	0.0, 34.0	1.0, 34.0	0.0, 34.0
Time to discharge from initiation of PCI (days)			
N (Missing)	37(3)	19(1)	56(4)
Mean(S,D)	1.9(5.4)	5.2(10.3)	3.0(7.5)
Median(25 <sup>th</sup> , 75 <sup>th</sup> )	1.0(1.0, 1.0)	1.0(1.0, 1.0)	1.0(1.0, 1.0)
Minimum, Maximum	1.0, 34.0	1.0, 34.0	1.0, 34.0



**Claims**

1. A method of improving or promoting patient recovery from trauma comprising administering a therapeutically effective amount of a vitamin B6 related compound.
2. The method according to claim 1, wherein the trauma is caused by an adverse physiological event selected from a group consisting of: myocardial infarction, myocardial ischemia, ischemic stroke, hemorrhagic stroke, major cardiac trauma, hypertension, arteriosclerosis, aneurysm, and congestive heart failure.
3. The method according to claim 1, wherein the trauma is caused by a traumatic contact to the patient, said traumatic contact selected from a group consisting of: abrasion, incision, contusion, puncture, compression, chemical burn, radiation burn, heat burn, and cold burn.
4. The method according to claim 1 wherein the trauma is surgical trauma resulting from the patient undergoing a surgical procedure.
5. The method according to claim 4, wherein the surgical procedure is selected from a group consisting of: coronary bypass surgery, biopsy, heart valve replacement, atheroectomy, thrombectomy, transcatheter vascular therapy, angioplasty, vascular grafting, placement of a mechanical shunt, placement of an intravascular stent, and organ transplantation.
6. The method according to claim 1, wherein the vitamin B6 related compound is selected from a group consisting of pyridoxine, pyridoxal, pyridoxal-5'-phosphate, pyridoxamine, a 3-acylated analogue of pyridoxal, a 3-acylated analogue of pyridoxal-4,5-aminal, a pyridoxine phosphate analogue, and a mixture thereof.
7. The method according to claim 1, wherein the vitamin B6 related compound is pyridoxal-5-phosphate.

8. The method according to claim 6, wherein the 3-acylated analogue of pyridoxal is:



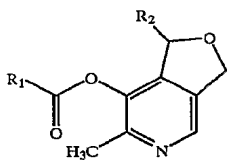
wherein,

$R_1$  is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxycarbonyl, or

$R_1$  is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxycarbonyl; dialkylcarbamoyloxy; or

$R_1$  is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

9. The method according to claim 6, wherein the 3-acylated analogue of pyridoxal-4,5-aminal is



wherein,

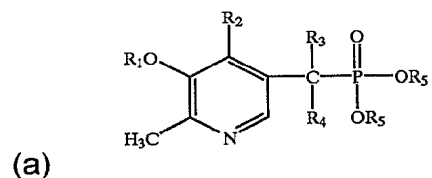
$R_1$  is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxycarbonyl, or

$R_1$  is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxycarbonyl; dialkylcarbamoyloxy; or

$R_1$  is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

$R_2$  is a secondary amino group.

10. The method according to claim 6, wherein the pyridoxine phosphate analogue is selected from a group consisting of:



wherein,

$R_1$  is hydrogen or alkyl;

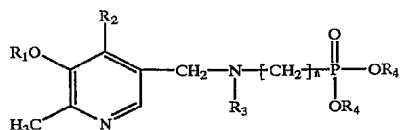
$R_2$  is  $-\text{CHO}-$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_3$ ,  $-\text{CO}_2\text{R}_6$  in which  $\text{R}_6$  is hydrogen, alkyl, aryl; or

$R_2$  is  $-\text{CH}_2-\text{O}$  alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of  $\text{R}_1$ ;

$\text{R}_3$  is hydrogen and  $\text{R}_4$  is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino, or arylamino; or

$\text{R}_3$  and  $\text{R}_4$  are halo; and

$\text{R}_5$  is hydrogen, alkyl, aryl, aralkyl, or  $-\text{CO}_2\text{R}_7$  in which  $\text{R}_7$  is hydrogen, alkyl, aryl, or aralkyl;



(b)

wherein,

$R_1$  is hydrogen or alkyl;

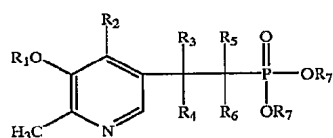
$R_2$  is  $-CHO$ ,  $-CH_2OH$ ,  $-CH_3$ ,  $-CO_2R_5$  in which  $R_5$  is hydrogen, alkyl, aryl; or

$R_2$  is  $-CH_2-O$  alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of  $R_1$ ;

$R_3$  is hydrogen, alkyl, aryl, aralkyl,

$R_4$  is hydrogen, alkyl, aryl, aralkyl, or  $-CO_2R_6$  in which  $R_6$  is hydrogen, alkyl, aryl or aralkyl;

$n$  is 1 to 6; and



(c)

wherein,

$R_1$  is hydrogen or alkyl;

$R_2$  is  $-CHO-$ ,  $CH_2OH-$ ,  $-CH_3$ ,  $-CO_2R_8$  in which  $R_8$  is hydrogen, alkyl, aryl; or

R<sub>2</sub> is -CH<sub>2</sub>-O alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R<sub>1</sub>;

R<sub>3</sub> is hydrogen and R<sub>4</sub> is hydroxy, halo, alkoxy, or alkanoyloxy; or

R<sub>3</sub> and R<sub>4</sub> can be taken together to form =O;

R<sub>5</sub> and R<sub>6</sub> are hydrogen; or

R<sub>5</sub> and R<sub>6</sub> are halo;

R<sub>7</sub> is hydrogen, alkyl, aryl, aralkyl, or -CO<sub>2</sub>R<sub>8</sub> in which R<sub>8</sub> is hydrogen, alkyl, aryl, or aralkyl.

11. The method according to claim 4, wherein the vitamin B6 related compound is administered prior to the patient undergoing the surgical procedure.

12. The method according to claim 11, wherein the vitamin B6 related compound is administered at least 4 hours prior to the patient undergoing the surgical procedure.

13. The method according to claim 11, further comprising the step of administering a therapeutically effective amount of the vitamin B6 related compound following the surgical procedure.

14. The method according to claim 1, wherein the vitamin B6 related compound is administered after the trauma takes place.

15. The method according to claim 1, wherein the therapeutically effective amount of vitamin B6 related compound is between 1 and 1000 mg per day.

16. The method according to claim 7, wherein the therapeutically effective amount of pyridoxal-5'-phosphate is between 5 and 50 mg/kg patient weight per day.

17. The method according to claim 16, wherein the therapeutically effective amount of pyridoxal-5'-phosphate is 10 mg/kg patient weight per day.

18. The method according to claim 4, further comprising administering a platelet aggregation inhibitor selected from a group consisting of: a thromboxane A2 inhibitors, a glycoprotein IIb/IIIa inhibitor, an adenosine phosphate inhibitor, a fibrinogen-platelet binding inhibitor, and a platelet c-AMP phosphodiesterase inhibitor.

19. The method according to claim 18 wherein the administration of platelet aggregation inhibitor is at a lower dosage than a standard dose that would be given in the absence of vitamin B6 related compound administration.

20. A method of improving the success rate of surgical procedures comprising administering a therapeutically effective amount of a vitamin B6 related compound.

21. The method according to claim 20 wherein the surgical procedure is selected from a group consisting of coronary bypass surgery, biopsy, heart valve replacement, atheroectomy, thrombectomy, trans catheter vascular therapy, angioplasty, vascular grafting, placement of a mechanical shunt, placement of an intravascular stent, and organ transplantation.

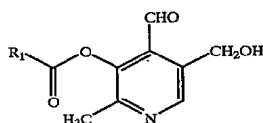
22. The method according to claim 21, wherein the organ transplantation is selected from a group consisting of a kidney transplant, a heart transplant, and a liver transplant.

23. The method according to claim 20, wherein the vitamin B6 related compound is selected from a group consisting of pyridoxine, pyridoxal, pyridoxal-5'-phosphate,

pyridoxamine, a 3-acylated analogue of pyridoxal, a 3-acylated analogue of pyridoxal-4,5-aminal, a pyridoxine phosphate analogue, and a mixture thereof.

24. The method according to claim 20, wherein the vitamin B6 related compound is pyridoxal-5-phosphate.

25. The method according to claim 23, wherein the 3-acylated analogue of pyridoxial is:



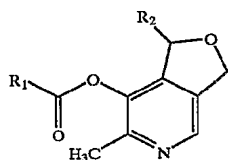
wherein,

R<sub>1</sub> is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxycarbonyl, or

R<sub>1</sub> is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxycarbonyl; dialkylcarbamoyloxy; or

R<sub>1</sub> is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

26. The method according to claim 23, wherein the 3-acylated analogue of pyridoxal-4,5-aminal is



wherein,

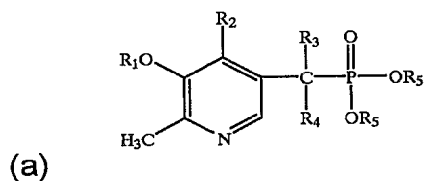
R<sub>1</sub> is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxycarbonyl, or

R<sub>1</sub> is dialkylcarbamoxyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxycarbonyl; dialkylcarbamoxyloxy; or

R<sub>1</sub> is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

R<sub>2</sub> is a secondary amino group.

27. The method according to claim 23, wherein the pyridoxine phosphate analogue is selected from a group consisting of:



wherein,

R<sub>1</sub> is hydrogen or alkyl;

R<sub>2</sub> is -CHO-, -CH<sub>2</sub>OH, -CH<sub>3</sub>, -CO<sub>2</sub>R<sub>6</sub> in which R<sub>6</sub> is hydrogen, alkyl, aryl; or

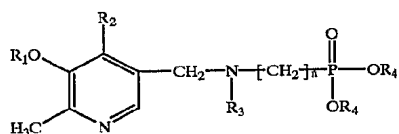
R<sub>2</sub> is -CH<sub>2</sub>-O alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of R<sub>1</sub>;



$R_3$  is hydrogen and  $R_4$  is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino, or arylamino; or

$R_3$  and  $R_4$  are halo; and

$R_5$  is hydrogen, alkyl, aryl, aralkyl, or  $-\text{CO}_2R_7$  in which  $R_7$  is hydrogen, alkyl, aryl, or aralkyl;



(b)

wherein,

$R_1$  is hydrogen or alkyl;

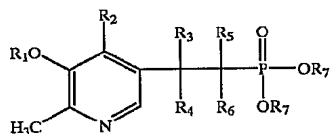
$R_2$  is  $-\text{CHO}$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_3$ ,  $-\text{CO}_2R_5$  in which  $R_5$  is hydrogen, alkyl, aryl; or

$R_2$  is  $-\text{CH}_2-\text{O}$  alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of  $R_1$ ;

$R_3$  is hydrogen, alkyl, aryl, aralkyl,

$R_4$  is hydrogen, alkyl, aryl, aralkyl, or  $-\text{CO}_2R_6$  in which  $R_6$  is hydrogen, alkyl, aryl or aralkyl;

$n$  is 1 to 6; and



(c)

wherein,

R<sub>1</sub> is hydrogen or alkyl;

R<sub>2</sub> is -CHO-, CH<sub>2</sub>OH-, -CH<sub>3</sub>, -CO<sub>2</sub>R<sub>8</sub> in which R<sub>8</sub> is hydrogen, alkyl, aryl; or

R<sub>2</sub> is -CH<sub>2</sub>-O alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R<sub>1</sub>;

R<sub>3</sub> is hydrogen and R<sub>4</sub> is hydroxy, halo, alkoxy, or alkanoyloxy; or

R<sub>3</sub> and R<sub>4</sub> can be taken together to form =O;

R<sub>5</sub> and R<sub>6</sub> are hydrogen; or

R<sub>5</sub> and R<sub>6</sub> are halo;

R<sub>7</sub> is hydrogen, alkyl, aryl, aralkyl, or -CO<sub>2</sub>R<sub>8</sub> in which R<sub>8</sub> is hydrogen, alkyl, aryl, or aralkyl.

28. The method according to claim 20, wherein the vitamin B6 related compound is administered prior to the patient undergoing the surgical procedure.

29. The method according to claim 28, wherein the vitamin B6 related compound is administered at least 4 hours prior to the patient undergoing the surgical procedure.

30. The method according to claim 28, further comprising the step of administering a therapeutically effective amount of the vitamin B6 related compound following the surgical procedure.

31. The method according to claim 20, wherein the vitamin B6 related compound is administered after the trauma takes place.

32. The method according to claim 20, wherein the therapeutically effective amount of vitamin B6 related compound is between 1 and 1000 mg per day.
33. The method according to claim 24, wherein the therapeutically effective amount of pyridoxal-5'-phosphate is between 5 and 50 mg/kg patient weight per day
34. The method according to claim 33, wherein the therapeutically effective amount of pyridoxal-5'-phosphate is 10 mg/kg patient weight per day.
35. The method according to claim 20, further comprising administering a platelet aggregation inhibitor selected from a group consisting of: a thromboxane A2 inhibitors, a glycoprotein IIb/IIIa inhibitor, an adenosine phosphate inhibitor, a fibrinogen-platelet binding inhibitor, and a platelet c-AMP phosphodiesterase inhibitor.
36. The method according to claim 35 wherein the administration of platelet aggreghan inhibitor is at a lower dosage than a standard dose that would be given in the absence of vitamin B6 related compound administration.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2005/001387

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC(7): A61K 31/675, A61K 31/4415

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
A61K 31/675 A61K 31/4415

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
A61K

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)  
Delphion, espacenet, USPTO, PubMed, Scopus, internet, Canadian Patent DB.  
Pyridox\*, pyridoxal, healing, surgery, vitamin B6, trauma.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Traumogen (R); Product Fact Sheet, (2002) [Thorne Research Inc.] Available from <a href="http://www.kombuchapower.com/traumogen1.pdf">http://www.kombuchapower.com/traumogen1.pdf</a> (See entire document)	1-7, 11-24, 28-36
X	Indian J. Exp. Biol., Vol 33(4), pp 278-280. (04-1995) [Udupa] <i>Inhibition of lysyl oxidase by isoniazid and its effect on wound healing.</i> (See: Abstract)	1-7, 11-24, 28-36
X	US 6,586,414 (01-07-2003) [Haque et al.] <i>Treatment of Cerebrovascular disease.</i> (See: entire document, especially column 4, line 12-15)	1-2, 4-36
X	WO 01/64692 (07-09-2001) [Haque] <i>Cardioprotective phosponates and malonates</i> (See: entire document, especially page 7, lines 28-32)	20-36

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 October 2005 (17-10-2005)

Date of mailing of the international search report

28 November 2005 (28-11-2005)

Name and mailing address of the ISA/CA  
Canadian Intellectual Property Office  
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2005/001387

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. Fr. Ophthalmol., Vol 10(1), pp 35-40 (1987) [Rivaud et al.] <i>Monobloc lamellar autokeratoplasty (MLAK) and corneal cicatrization. Apropos of a comparative trial in a control group and a group treated with a L-cystine and pyridoxine hydrochloride combination.</i> (See: entire document)	1-7, 11-24, 28-36
Y	Arq. Cent. Estud. Curso. Odontol., Vol 25-26(1-2), pp 28-34 (12-1988/01-1989) [de Lucia et al.] <i>(Tooth extraction wound healing after administration of vitamin B6 (pyridoxine). Histological study in rats.)</i> (See: entire document)	1-7, 11-24, 28-36
Y	Clinical Chemistry, Vol 49(3), (01-03-2003) [Talwar et al.] <i>(Pyridoxal phosphate decreases in plasma but not erythrocytes during systemic inflammatory response.)</i> (See: entire document, especially first 2 sentences)	1-7, 11-24, 28-36
Y	Alternative Medicine Review, Vol 6(1), (2001) [Thorne Research Inc.] Vitamin B6 (Pyridoxine; Pyridoxal 5'-Phosphate) (See: entire document, especially introduction)	1-7, 11-24, 28-36

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2005/001387

## **Box No. II**      **Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 1-36  
because they relate to subject matter not required to be searched by this Authority, namely :  
  
Claims 1-36, directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 1-36.
2. ☐ Claim Nos. :  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :
3. ☐ Claim Nos. :  
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## **Box No. III**      **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows :

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

**Remark on Protest** ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.  
PCT/CA2005/001387

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US6586414	01-07-2003	AU4870301 A	08-10-2001
		CA2404329 A1	04-10-2001
		EP1278526 A2	29-01-2003
		JP2003528146T T	24-09-2003
		US6861439 B2	01-03-2005
		US2004121988 A1	24-06-2004
		WO0172309 A2	04-10-2001
WO0164692	07-09-2001	AT293119T T	15-04-2005
		AU3718501 A	12-09-2001
		CA2401655 A1	07-09-2001
		DE60110054D D1	19-05-2005
		DK1268498T T3	08-08-2005
		EP1268498 A1	02-01-2003
		EP1531157 A1	18-05-2005
		JP2003525303T T	26-08-2003
		PT1268498T T	29-07-2005
		US6605612 B2	12-08-2003
		US6667315 B2	23-12-2003
		US6780997 B2	24-08-2004
		US6867215 B2	15-03-2005
		US2003114677 A1	19-06-2003
		US2004171588 A1	02-09-2004